

Investigation of *ABCA1* C69T polymorphism in patients with type 2 diabetes mellitus

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Abstract

Introduction: Non insulin dependent diabetes mellitus is the most common type of diabetes. Genetic factors, lipid profiles, hypertension are potential risk factors for diabetes mellitus. Adenosine binding cassette transporter proteins 1 (*ABCA1*) plays a role in cholesterol metabolism, especially high density lipoprotein (HDL-cholesterol). There are multiple mechanisms by which HDL-cholesterol can be atheroprotective, it is clear that the relative activity of *ABCA1* plays a major role. We aimed to investigate association of *ABCA1* C69T gene polymorphism with lipid levels in Turkish type 2 diabetic patients.

Materials and methods: After isolation of DNA by ethanol precipitation we determined *ABCA1* gene polymorphism by using polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method in 107 type 2 diabetic patients and 50 healthy controls.

Results: We have observed that the frequency of TT genotype is significantly higher in healthy controls compared to patients (14% vs. 3%; $P = 0.008$). Also frequency of T allele was higher in controls than in patients (34% vs. 21%; $P = 0.020$; OR (95% CI) = 0.52 (0.30-0.88)). There was no association of lipid levels and *ABCA1* C69T polymorphism subgroups.

Conclusion: We have found significantly higher frequency of both T allele and genotype in control group when compared to patients that made us think that T allele may be a protective factor against diabetes mellitus. But, we could not find a relationship between genotypes and lipid concentrations in our two groups. Larger studies will help us to understand the relationship between *ABCA1* C69T genotype and lipid parameters in diabetes mellitus.

Key words: diabetes mellitus; lipoproteins; high density lipoprotein; dyslipidemia; polymorphism, genetic

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Introduction

Type 2 diabetic patients exhibit dyslipidemia with high triglyceride and low high density lipoprotein (HDL-cholesterol) concentration which are the underlying pathology behind cardiovascular disease (1,2). Numerous population studies have shown an association between plasma lipid levels and coronary artery disease risk (3,4). Moreover, epidemiological studies suggest that the risk of developing coronary heart disease for patient with diabetes mellitus is 2–4 times higher than their counterparts without diabetes (1). Some experimental studies suggested that accumulation of cholesterol in islets causes to reduced glucose-stimulated

insulin secretion (GSIS), and impaired glucose tolerance in mice. Therefore elevated cholesterol levels may be a risk factor for glucose intolerance and diabetes (5).

Adenosine binding cassette transporter proteins 1 (*ABCA1*) plays a role in cholesterol metabolism, especially HDL-cholesterol. Previous investigations showed that homozygous mutations in the *ABCA1* gene cause Tangier disease and heterozygosity causes for familial hypoalphalipoproteinemia. There are multiple mechanisms by which HDL-cholesterol can be atheroprotective, it is clear that the relative activity of *ABCA1* plays a major role.

Genetic and molecular biology studies have suggested that low plasma HDL-cholesterol concentration in many individuals reflect an impaired ABCA1 pathway, which would also promote the accumulation of cholesterol in tissue macrophages. Albrecht *et al.* showed that *ABCA1* gene expression was significantly elevated in atherosclerotic plaques (6). Porchay *et al.* suggested that *ABCA1* gene polymorphisms modulate HDL-cholesterol concentrations in an interaction with body mass index (BMI), and thus, they might influence cardiovascular risk in the general population (7). In addition, *ABCA1* R230C polymorphism was shown to be associated with a 4-fold occurrence of diabetes and it may have an important role in maintaining glucose-mediated insulin secretion (8). Salinas *et al.* reported that the absence of ABCA1 led to cholesterol accumulation within the beta cell plasma membrane, suggesting that ABCA1 may be not only a determinant of HDL-cholesterol but also a link among diabetes, metabolic syndrome and atherosclerosis (9). In another study, the authors have demonstrated that high glucose can suppress the mRNA expression of ABCA1 in mouse primary peritoneal macrophages (10).

There were fewer investigations about the role of *ABCA1* C69T polymorphism (rs1800977) in lipid related disorders such as diabetes, cardiovascular disease etc. According to these knowledge, we aimed to investigate the relationship between *ABCA1* C69T gene polymorphisms and lipid concentrations in Turkish type 2 diabetic patients.

Materials and methods

Study design and subjects

Our investigation was a case-control study. The patient group consisted of 107 patients (median = 56 years; min-max = 25-85 years; 71 females and 36 males) with type 2 diabetes. The patients were recruited from Department of Internal Medicine, Haseki Training and Research Hospital between in the period from 2009 to 2011. Patients were diagnosed with diabetes mellitus based on the fasting blood glucose concentration (> 7 mmol/L) (11). Systemic arterial hypertension was considered to be present if the SBP was > 130 mm Hg and/or DPB was > 90 mm Hg.

The control group was selected from patients attending the general surgery and orthopedic clinics of the same hospital and who were treated for trauma. BMI (weight in kilograms divided by the square of the height in meters) values were calculated retrospectively and categorized according to World Health Organization recommendations (12). The smoking status of an individual was assigned 'yes' if they were smoking currently or had given up < 3 months previously. The control group was selected from patients without type 2 diabetes and with negative family history of diabetes mellitus. It consisted of 50 individuals (median = 49 years; min-max = 29-85 years; 17 females and 33 males).

This study was approved by the Ethical Committee of Istanbul University, The Istanbul Faculty of Medicine. All of participants, after giving written informed consent, completed a structured questionnaire in order to collect demographic data.

Determination of biochemical parameters

After overnight fasting, blood samples were drawn in plain tubes (Vacuette, Greiner Labor technik, Germany). One plain tube was used for each subject. The samples were centrifuged for 10 min at $1,500 \times g$ at room temperature, followed by the removal of serum. Serum was stored at -20°C , until concentrations of triglycerides, total cholesterol and fasting blood glucose were determined by using Hitachi 717 autoanalyzer (Tokyo, Japan). Concentrations of HDL-cholesterol were measured subsequently after precipitation of ApoB-containing lipoproteins with phosphotungstic acid/ MgCl_2 . LDL-C concentration was calculated using the Friedewald formula when the triglyceride concentration was < 4 mmol/L; otherwise, LDL-C concentration was measured directly using the Hitachi 717 autoanalyzer (Tokyo, Japan) (13,14).

Isolation of DNA

Blood specimens were collected in tubes containing EDTA (Vacuette, Greiner Labor technik, Germany) and DNA was prepared from the leukocyte pellets by sodium dodecyl sulphate lysis (Sigma Aldrich, Taufkirchen, Germany), ammonium acetate (Sigma Aldrich, Taufkirchen, Germany) extraction and ethanol (Sigma Aldrich, Taufkirchen, Germany) precipitation (15). One tube containing

EDTA was used for each subject. DNA samples were stored at +4 °C until PCR application.

Determination of ABCA1 C69T gene polymorphism

Gene polymorphisms were determined using following PCR-RFLP method (16). Template DNA (0.5–1.0 µg) was used in a PCR under stringent conditions to avoid the possibility of false positives for C69T genotyping. Reactions were performed with 10 pmol of each primer (Invitrogen, Grand Island, USA): forward primer 5' CAG CGC TTC CCG CGC GTC TTA 3', reverse primer 5'CCA CTC ACT CTC GTC CGC AAT TAC 3' in final volume of 25 µL containing 1.5 mM MgCl₂, 50 mM KCl, 10 mM Tris-HCl (pH 8.4), 100 µmol/L of each dNTP (Invitrogen, Grand Island, USA) and 1 unit Taq Polymerase (Invitrogen, Grand Island, USA). Amplification was carried out in a DNA Thermal Cycler (Applied Biosystems, Carlsbad, USA) for 33 cycles with denaturation steps at 94 °C for 1 minute, annealing at 60 °C for 1 minute and extension at 72°C for 2 minutes. PCR products were separated on 2% agarose gel and DNA was visualized by ethidium bromide (Invitrogen, Grand Island, USA) staining. Presence of the polymorphisms was determined by enzymatic digestion of the initial PCR product with *BsmAI* (Invitrogen, Grand Island, USA) at 37 °C for 2h. Three genotypes could be determined after electrophoresis: genotype CC (345 bp band), genotype TT (310 bp band) and genotype CT (both bands).

Statistical analysis

Allele and genotype frequencies were determined by direct counting. Categorical variables such as genotypes and alleles were compared using Chi-Square (χ^2) test and z-test. Differences in continuous variables between carriers and control subjects were tested using Student's *t* test, except for creatinine, which was not normally distributed. Differences in creatinine and continuous outcome variables between carriers and control subjects were tested using the nonparametric Mann-Whitney *U* test (17).

Statistical analyses were performed with SPSS for Windows standard version 7.5 software (SPSS Inc, Chicago, USA). A *P* value of 0.05 was accepted as the threshold for defining statistical significance.

Results

Demographic characteristics are summarized in table 1. Total cholesterol (*P* = 0.001), triglycerides (*P* = 0.001), LDL-cholesterol (*P* = 0.001), VLDL-cholesterol (*P* = 0.001), systolic blood pressure (SBP) (*P* = 0.001), diastolic blood pressure (DBP) (*P* = 0.001), fasting blood glucose (*P* = 0.001) and total cholesterol/HDL- cholesterol levels (*P* = 0.001), body mass index (*P* = 0.003) and frequency of hypertension (*P* = 0.001) were higher in patients than in control subjects.

Frequencies of ABCA1 C69T polymorphism

Patient and control groups were in Hardy-Weinberg equilibrium for ABCA1 C69T genotypes (*P* = 0.310 and *P* = 0.440 respectively).

Distributions of C69T genotypes and alleles in study groups are shown in table 2. We have observed that the frequency of TT genotype is significantly higher in healthy controls compared to patients (14% vs. 3%; *P* = 0.008). Also frequency of T allele was higher in controls than in patients (34% vs. 21%; *P* = 0.020; OR (95% CI) = 0.52 (0.30–0.88)).

Relationship between polymorphism and plasma lipid levels

We could not find any relationship between ABCA1 C69T genotypes and lipid profiles. No association was found in HDL-cholesterol concentration according to the genotypes (Table 3).

Discussion

ABCA1 has an important role in the reverse transport of cholesterol from peripheral tissues to the liver via HDL-cholesterol. Mutations in *ABCA1* gene may induce several lipid transport defects of HDL-cholesterol (18). Numerous of studies on the relationship between *ABCA1* and diabetes mellitus have been done in recent times. Vergeer *et al.* showed that heterozygous carriers of *ABCA1* mutations displayed mild hyperglycemia with no difference in insulin response after an oral glucose challenge compared with noncarriers of similar age, sex, and BMI (19). In another study, Patel *et al.* indicated that ABCA1 expression and protein concentrations in leukocytes, as well as function in cul-

TABLE 1. Demographic characteristics of the study population.

	Type 2 diabetes (N = 107)	Controls (N = 50)	P
Body mass index (kg/m ²)	27.45 ± 5.00	25.20 ± 3.83	0.003
Smoking (%)	23.4	24	0.930
Hypertension (%)	71.4	28	0.001
SBP (mmHg)	135.87 ± 17.53	123.80 ± 19.57	0.001
DBP (mmHg)	84.50 ± 10.52	74.90 ± 13.11	0.001
Triacylglycerol (mmol/L)	1.96 ± 1.10	1.23 ± 0.39	0.001
Total cholesterol (mmol/L)	5.49 ± 1.50	3.94 ± 0.71	0.001
HDL- cholesterol (mmol/L)	0.97 ± 0.24	0.98 ± 0.36	0.903
LDL- cholesterol (mmol/L)	3.67 ± 1.38	2.46 ± 0.67	0.001
VLDL- cholesterol (mmol/L)	0.91 ± 0.51	0.57 ± 0.18	0.001
Total cholesterol/ HDL- cholesterol	6.03 ± 2.40	4.40 ± 1.42	0.001
Fasting blood glucose (mmol/L)	9.85 ± 3.76	5.29 ± 1.41	0.001
Urea (mmol/L)	6.86 ± 3.29	7.99 ± 4.27	0.387
Creatinine (μmol/L)	78.67 (69.61-91.93)	79.56 (68.51-91.71)	0.946

TABLE 2. Distribution of ABCA1 C69T genotypes and alleles in study groups.

ABCA1 C69T	Patients (N = 107)	Controls (N = 50)	P	OR	95%CI
CC	65 (0.61)	23 (0.46)			
CT	39 (0.36)	20 (0.40)	0.360*	0.69	0.34-1.42
TT	3 (0.03)	7 (0.14)	0.008*	0.15	0.04-0.64
C	169 (0.79)	66 (0.66)	0.020**	0.52	0.30-0.88
T	45 (0.21)	34 (0.34)			

*Fisher exact test vs. CC genotype; **Chi-square test.

TABLE 3. Distribution of lipid levels according to ABCA1 C69T genotypes in study groups.

ABCA1 C69T genotypes	Patients (N = 107)					Controls (N = 50)				
	CC (N = 61)	TT (N = 5)	CT (N = 41)	Min-Max	P	CC (N = 23)	TT (N = 7)	CT (N = 20)	Min-Max	P
Triglycerides (mmol/L)	2.00 ± 1.00	2.08 ± 1.20	1.88 ± 1.19	0.56-6.41	0.908	1.16 ± 0.32	1.26 ± 0.58	1.31 ± 0.39	0.65-2.26	0.572
Total cholesterol (mmol/L)	5.48 ± 1.36	5.13 ± 3.42	5.54 ± 1.55	2.47-9.05	0.701	4.03 ± 0.64	4.23 ± 0.75	3.73 ± 0.75	1.91-5.15	0.504
HDL- cholesterol (mmol/L)	0.94 ± 0.23	0.88 ± 0.11	1.03 ± 0.25	0.34-1.71	0.669	1.04 ± 0.32	1.07 ± 0.49	0.88 ± 0.35	0.36-2.04	0.876
VLDL- cholesterol (mmol/L)	0.95 ± 0.53	1.01 ± 0.91	0.84 ± 0.43	0.26-2.90	0.831	0.53 ± 0.15	0.57 ± 0.26	0.60 ± 0.17	0.31-1.03	0.678
LDL- cholesterol (mmol/L)	3.64 ± 1.29	3.23 ± 2.61	3.77 ± 1.44	1.27-6.98	0.620	2.56 ± 0.70	2.58 ± 0.73	2.31 ± 0.63	0.93-3.83	0.920
Total Cholesterol /HDL- Cholesterol	6.21 ± 2.49	6.16 ± 4.81	5.75 ± 2.29	2.44-15.48	0.975	4.09 ± 1.05	4.43 ± 1.41	4.74 ± 1.75	1.68-8.29	0.577

tured skin fibroblasts, are reduced in type 2 diabetic patients (20). Brunham *et al.* reported that a new role for ABCA1 in mediating cholesterol homeostasis and insulin secretion in pancreatic β -cells. According to their results, ABCA1 was highly expressed in β -cells, and absence of β -cell ABCA1 resulted in accumulation of cellular cholesterol, marked reduction in insulin secretion *in vivo* and a progressive impairment in glucose tolerance. This result gives us important information about ABCA1 genes and diabetes risk (5). Gao *et al.* showed that reduction in the concentration of HDL-C may be responsible for accelerated atherosclerosis in diabetic patients with poor glycemic control (10).

In previous studies, a lot of ABCA1 polymorphisms were investigated in lipid related diseases such as coronary artery disease and diabetes mellitus (21,22).

In a previously published study, recently found frequent non-synonymous R230C variant within ABCA1 gene was associated with HDL-cholesterol concentration, obesity and type 2 diabetics in Mexican Mestizos. It was determined that cells expressing the C230 allele showed a 27% cholesterol efflux reduction confirming that this variant has a functional effect *in vitro*. Also, C230 allele was associated with lower HDL-cholesterol concentration and higher body mass index (23). Harada *et al.* provided an evidence that the I/M 823 variant, not the R/K 219 variant, in the ABCA1 gene is a determinant of the HDL-cholesterol level. In addition, these authors showed the importance of this gene on lipid metabolism in Japanese patients with CAD (24). Tregouet *et al.* found that the ABCA1 R219K variant is associated with myocardial infarction risk (25).

Liu *et al.* suggested that the -191 G/C SNP in the promoter region of the ABCA1 gene is associated with CAD (26). Hong *et al.* found that the ABCA1 G2265 T variant may lead to decreased HDL-cholesterol (27). Porchay-Baldérelli *et al.* observed that the M allele of the I883M SNP was associated with higher HDL-cholesterol concentration and also the minor allele of the +378GNC SNP was associated with lower HDL-cholesterol concentration in 3129

French people (28). Saleheen *et al.* found a novel mutation in ABCA1 gene associated with low HDL-cholesterol concentration and type 2 diabetes mellitus (29).

In current study we have investigated ABCA1 C69T polymorphism in type 2 diabetic patients. According to the previous studies, our first aim was to explore possible relationship between ABCA1 C69T polymorphism and lipid concentrations in diabetic patients. However, we did not find any relationship between lipid levels and C69T gene polymorphism in both study groups. Whereas, in our previous study, we observed that the C69T polymorphism was associated with HDL-cholesterol concentration (30). In another Turkish study, Hodoglugil *et al.* evaluated polymorphisms in the ABCA1 gene in Turks, which is a population characterized by low HDL-cholesterol concentration. They observed that rare alleles of the C14T and V771M polymorphisms were associated with higher HDL-cholesterol concentration in men (31).

However, similarly to our results, some studies have reported no association between ABCA1 polymorphisms and lipid profile. Finnish Study suggested that the ABCA1 locus was not linked to HDL-cholesterol concentration in the coronary heart disease (32).

Nevertheless, we have found significantly higher frequency of both T allele and genotype in control group when compared to patients that made us think that T allele may be a protective factor against diabetes mellitus. But, we could not a relationship between genotypes and lipid concentrations in our two groups.

The present study has some potential limitations, the small number of study groups being the most important one. This could be a reason for some of the results that demonstrated no statistical significance. Studies with a larger sample size in different races will help us to understand relationship between ABCA1 C69T polymorphism and lipid parameters in diabetes mellitus.

Potential conflict of interest

None declared.

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Ispitivanje polimorfizma *ABCA1* C69T kod bolesnika sa šećernom bolesti tipa 2

Sažetak

Uvod: Šećerna bolest tipa 2 najčešći je tip šećerne bolesti. Genetski faktori, lipidni status i povišeni krvni tlak predstavljaju potencijalne čimbenike rizika za razvoj šećerne bolesti. Adenozin-trifosfat vezujući kasetni protein (engl. *adenosine binding cassette transporter proteins 1*, *ABCA1*) ima ulogu u metabolizmu kolesterola, a posebno kod HDL-kolesterola. Postoje višestruki mehanizmi kojim HDL kolesterol može predstavljati zaštitu od stvaranja plaka te je jasno da pritom relativna aktivnost *ABCA1* igra veliku ulogu. Naš je cilj bio istražiti povezanost polimorfizma *ABCA1* C69T s koncentracijom lipida kod Turskih bolesnika oboljelih od šećerne bolesti tipa 2.

Materijali i metode: Nakon izolacije DNA metodom taloženja u etanolu, polimorfizam C69T gena *ABCA1* određen je kod 107 ispitanika oboljelih od šećerne bolesti tipa 2 i 50 zdravih ispitanika primjenom metode lančane reakcije polimerazom – polimorfizma restrikcijskih fragmenata na osnovi njihove duljine (engl. *polymerase chain reaction- restriction fragment lenght polymorphism*, PCR-RFLP).

Rezultati: Istraživanje je pokazalo da je učestalost TT genotipa statistički značajno viša kod kontrolnih ispitanika u usporedbi sa skupinom bolesnika (14% vs. 3%; $P = 0,008$). Također, frekvencija T alela bila je viša kod kontrolnih ispitanika nego kod ispitanika sa šećernom bolesti (34% vs. 21%; $P = 0,020$; OR (95% CI) = 0,52 (0,30–0,88)). Nije bilo povezanosti između koncentracije lipida i polimorfizma *ABCA1* C69T.

Zaključak: Pronašli smo visoke učestalosti T alela i TT genotipa kod kontrolne skupine u usporedbi s bolesnicima sa šećernom bolesti, što nas navedi na zaključak da je T alel protektivan čimbenik za šećernu bolest. Međutim, nismo mogli naći vezu između genotipova i koncentracije lipida u naše dvije skupine ispitanika. Daljnja će istraživanja pomoći u razumijevanju veze između genotipa *ABCA1* C69T i lipidnih parametara kod šećerne bolesti.

Ključne riječi: šećerna bolest; lipoproteini; lipoprotein visoke gustoće; dislipidemija; genetski polimorfizam